8.9 A High-Density Magnetoresistive Biosensor Array with Drift-Compensation Mechanism

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DNA microarrays are under intense development for a wide range of applications in molecular biology research and clinical diagnostics. The most common technique uses fluorescent labels, which are detected with laser scanners. The required instrumentation, however, needs to be reduced in size and cost to realize a hand-held device. Magnetoresistive sensors are now employed as bio-sensing devices because of their high sensitivity [1]. They are compatible with CMOS processing, and can easily be integrated with a CMOS chip to form a lab-on-a-chip system [2].

In the magnetoresistive microarray, single-stranded DNA with a known sequence is immobilized on the sensor surface through a sulfur-Au linkage. The biotinlated analyte DNA is then selectively captured by complementary probes. Streptavidin coated magnetic labels are added and bind to the hybridized DNA. The stray magnetic field of the magnetic labels is detected as a resistance change in the sensor. Figure 8.9.1 shows the device integration with CMOS chips.

Nanometer-scale sensors provide high sensitivity for an individual sensor; however, the mass transport effect limits the overall sensitivity [3]. A multidivided array structure is designed to enhance the overall sensitivity by combining several sensor pixels per biological sample spot. With this structure, the molecular diffusion time is largely reduced, and statistical methods can be applied to further increase the detection accuracy. Figure 8.9.2 shows the system architecture. The 2mm×2mm chip is designed using a 0.25μm BiCMOS technology. Each subarray occupies an area of 120μm×120μm, and all 16 DNA spots share the same control bus. The signals from the biosensors are purely analog. Thus, when designing the sensor-select switches, both linearity and noise must be considered. Although the same functionality can be achieved with the 1T cell addressing approach commonly used in memory design, that approach suffers from large 1/*f* noise coming from the MOS switch and undesired signal modulation caused by the modification of the on-resistance of the transistor. Figure 8.9.2 shows a modified 2T-1-spin-valve (2T1SV) cell design that provides a solution to both of the above issues. Provided that the output resistance of the current source is much larger than the sensor resistance, the flicker noise from both the row and column switches will appear highly attenuated at the output as a result of the resistive division. To reduce the read-out time of this high-density array, we apply both frequency-division multiplexing (FDM) and time-division multiplexing (TDM) schemes.

Figure 8.9.3 shows the circuit design of the readout channel. To cancel offsets of sensor pairs, digitally programmable current sources are included and adjusted in a calibration sequence. A single 42kHz master clock is used to generate 4 carrier frequencies from the clock circuitry. This modulation provides FDM and shifts the signal spectrum up so that 1/f noise in the following circuit is unimportant. The modulation also separatess the desired signals from electromagnetic interference (EMI), which is essential in our detection method. The nonidealities of the passive double-balanced mixer, which include clock feedthrough and charge injection, can be minimized using a short transition time with half-sized dummy switches. The dummy switches are driven by complementary clock signals from the main switches, and serve as local charge sinks (or providers) to compensate for the injected charges. A fully differential structure is also designed so that the injected charges appear as a common-mode signal only. The input-referred noise of the LNA is below 50nV/√Hz over the frequency range of interest. An instrumentation amplifier with a digitally controlled gain is designed to maximize the dynamic range of the system.

Another issue for low concentration bio-detection is the potential false positive caused by drifts or ionic solution interference when differentiating signals before and after biological reaction. A high signal-to-noise ratio is insufficient to determine the resolution of biochips. We address this issue through a novel detection method called dual-bias double-modulation (DBDM). The magnetic field configuration is shown in Fig. 8.9.4, and the output from the biochip can be written as in Equation (1) in the figure. I is the bias current, A is the total gain, ΔR_{max} is the maximum resistance change of the sensor, θ_f is the angle between the easy axis and the magnetization of the free layer, and EMI is generated by the AC in-plane magnetic field. The drift was compensated by alternating the amplitude of the DC bias field along the easy axis of the spin valves. Assuming the drift or ionic solution interference has a slow change, which can be neglected within each bias-field cycle period, we take the ratio of the signal at the low bias field to the signal at the high bias field as our signal of interest, see Equation (2) in the figure. The EMI is separated from the other terms by the on-die mixer; thus, only the magnetization configuration term will be left after taking the ratio, and this term is only sensitive to the change of the magnetic fields generated by nanoparticles. The final biological signal is the difference between these ratios before and after magnetic nanoparticles are applied, which is shown in Equation (3) in the figure. In Fig. 8.9.5, the FFT of a single FDM channel is displayed. The input-referred noise is below 55nV/√Hz for the frequency band of interested (>3kHz). P-poly resistors were also incorporated in each sub-array to evaluate the functionality and performance of the circuit. Figure 8.9.5 shows double modulation using both the AC magnetic field (208Hz) and the on-die mixer (5.25kHz). Side tones at 5458Hz and 5042Hz are only observed when measuring the magnetic sensor, which confirms the separation of the EMI and signal tones. To demonstrate the buffer interference cancelling ability of the DBDM method, we rinsed the chip with a phosphate buffered saline (PBS) buffer and compared the side tones with and without DBDM (Fig. 8.9.6). Clearly, the signal became insensitive to the presence of the buffer solution when we applied DBDM. The on-die temperature controller is also designed to actively control the biochip temperature for the biological reaction (Fig. 8.9.4). We used an NPN transistor as a temperature sensor, and from the simulation, dV_{be}/dT = -1.375 mV/°C for I_c = 200μA.

Surface modification of the biochip followed the procedure established by Herne and coworkers [4]. The DNA surfaces were prepared by placing the chip in a 1.0M KH_2PO_4 buffer solution of 1μM DNA overnight. After water rinse, the chip was then immersed into a 1mM mercaptoundecanoic acid for 1hr. Hybridization was performed with 20μL target DNA in a morpholineethanesulfonic acid (MES) buffer (0.3M NaCl, pH 6.5) for 1 hr; afterwards, the chip was rinsed with a PBS buffer and water. Before applying particles, the surface was blocked with 1% Bovine serum albumin (BSA) in PBS buffer for 10min, rinsed with PBS. SEM images (Fig. 8.9.7) show high contrast between complementary and noncomplementary DNA spots. A real-time measurement shows about 4μV signal change after nanoparticle absorption (with target DNA of 10nM).

Acknowledgments:
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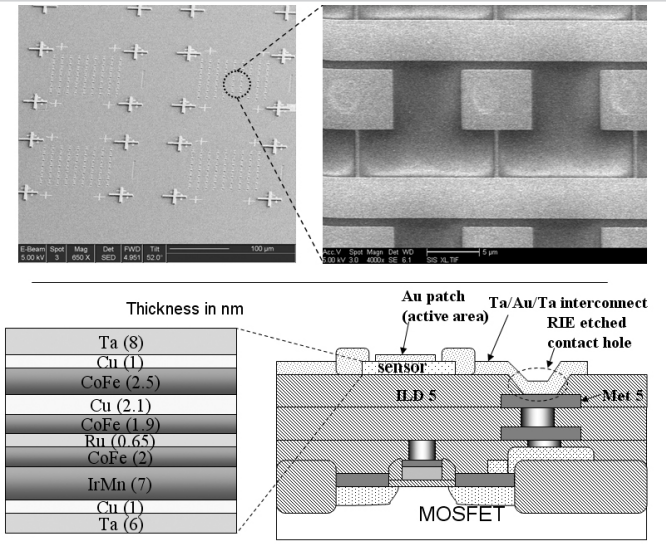

Figure 8.9.1: (Top) Nanometer-size magnetic biosensor array. (Bottom) Schematic drawing of sensor integration with CMOS chip.

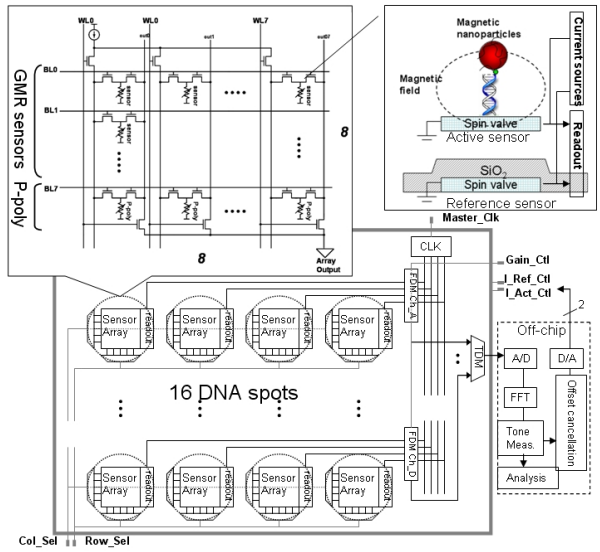

Figure 8.9.2: Magnetoresistive biosensor array chip architecture.

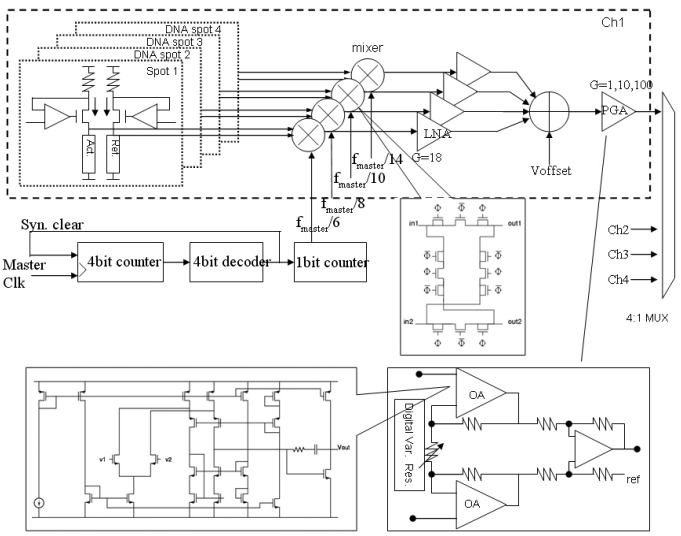

Figure 8.9.3: Analog front-end readout channel.

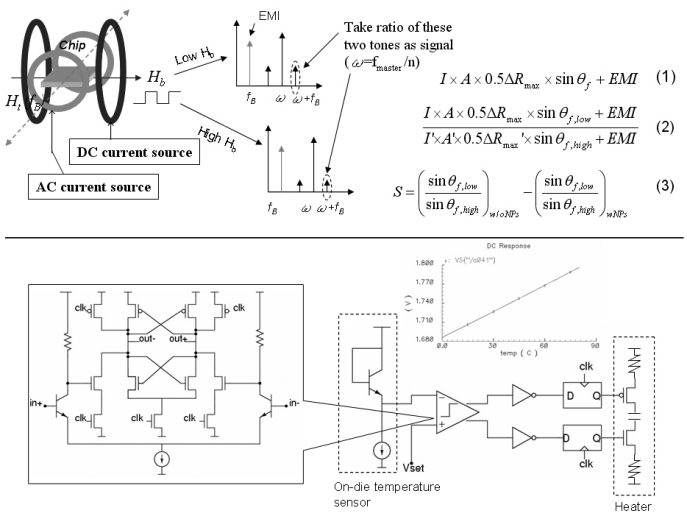

Figure 8.9.4: (Top) Dual-bias double modulation detection principle. (Bottom) On-die temperature controller design.

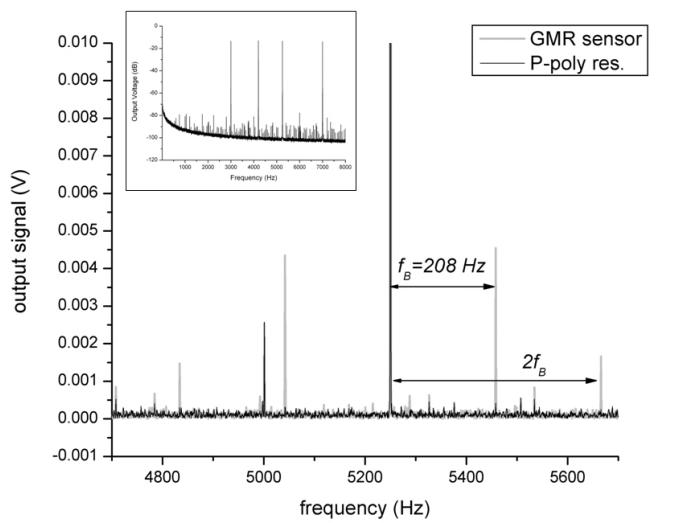

Figure 8.9.5: FDM output and double modulation.

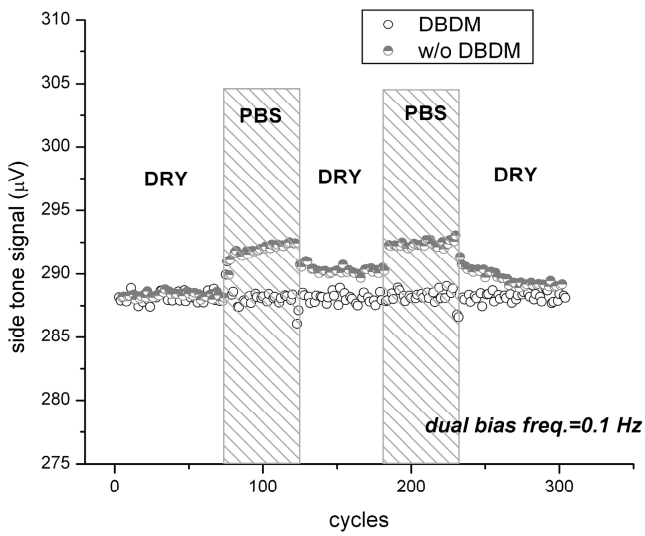

Figure 8.9.6: Ionic solution interference cancellation by the DBDM method.

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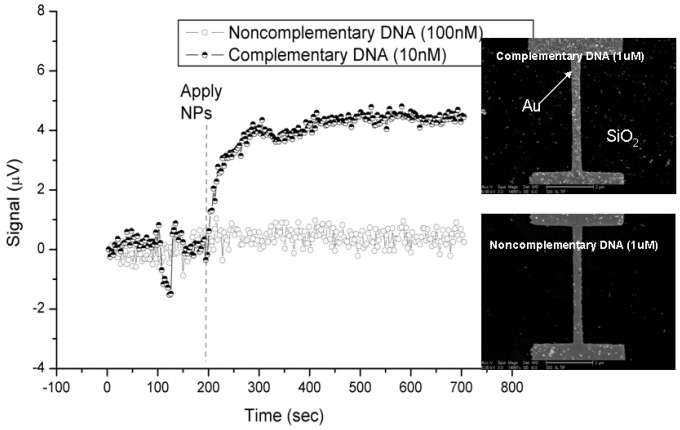

Figure 8.9.7: Measured signal for 10nM target DNA. SEM images ofparticle coverage on complementary and non-complementary DNA spots.

